REMARKS

This is meant to be a complete response to the Office Action mailed April 25, 2003, and a Summary of the Interview between the Examiner and Applicants' representatives Douglas Sorocco, Kathryn Hester and Mike Smith on October 8, 2003.

In the Office Action, the Examiner objected to the title of the invention as being non-descriptive, and objected to claims 42 and 88 for encompassing non-elected subject matter. The title has been amended herein to more accurately describe the invention being claimed, and claims 42 and 88 have been amended herein to delete references to SEQ ID NO:25. Therefore, Applicants respectfully request reconsideration and withdrawal of the objections to the title and to claims 42 and 88.

Claims 24, 42 and 88 were rejected under 35 U.S.C. 112, ¶1. In addition, the Examiner rejected Applicants' claims 24, 42 and 88 under 35 U.S.C. 102(a) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over McCourt et al. (Hepatology 30:1276). Further, the Examiner rejected Applicants' claims 24, 42 and 88 under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Yannariello-Brown et al. (Glycobiology 7:15).

Applicants' Response to the 35 U.S.C. 112, ¶1 Rejection

In the Office Action, the Examiner rejected claims 24, 42 and 88 under

35 U.S.C. 112, ¶1, for the following reason: "the specification, while being enabling for complete HARE 175, and fragments of HARE 175, is not enabling for HARE 'comprising a sequence essentially as set forth in SEQ ID NO:2' " (Office Action, Page 2, lines 25-26).

Claims 24, 42 and 88 have been amended in this application to recite a purified mammalian HARE comprising a protein which is able to specifically bind at least one of HA, chondroitin and chondroitin sulfate or a purified composition comprising a functionally active HARE polypeptide, wherein the protein or functionally active HARE polypeptide is purified to a state capable of being sequenced and comprises a sequence **having at least about 76% sequence identity to** SEQ ID NO:2.

Support for the amendments to the claims can be found in Paragraphs **[0061]** and **[0162]** and Figure 35 of the Specification. Therefore, Applicants respectfully submit that claims 24, 42 and 88 are definite and particularly point out and distinctly claim that which Applicants regard as the invention; that such claims reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention; and that such claims enable a person having ordinary skill in the art to make and use the invention.

Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. 112, ¶1 rejection of the claims.

Applicants' Response to the 35 U.S.C. 102(a)/103(a) Rejection of the Claims

In the Office Action, the Examiner maintained the rejection of Applicants' claims 24, 42 and 88 under 35 U.S.C. 102(a) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over McCourt et al., Hepatology 30:1276. In support of maintaining the rejection after submission of the 37 C.F.R. 1.132 declaration by Paul Weigel, the Examiner stated:

> Applicants argue in paper number 15, submitted 2/13/03, that because the McCourt reference was *accepted* for publication after the Zhou reference was *received* for publication, that there is demonstration of conception and constructive reduction to practice of the present invention prior to the publication date of the McCourt et al. reference. This argument has been fully considered but is not deemed persuasive as receipt for publication merely denotes when the first draft was submitted. It is not evidence as to what that first draft contained. It is common in the art for publications to undergo substantial revision between the first submitted draft and the published manuscript, often including additional experimentation. In view of such, the mere date of submission of the first draft cannot be relied upon to establish conception and reduction to practice. Applicants may wish to resolve this issue by submission of an additional declaration under 37 C.F.R. 1.131 by the inventor, submitting a copy of the manuscript as it was submitted on that date, or alternatively stating that the published version was the same as that submitted on 7/25/99.
> *Office Action*, Page 5, line 30 - Page 6, line 7

Applicants respectfully traverse the rejection of pending claims 24 and 42 based on the 37 CFR 1.132 declaration attached hereto. The declaration, signed by co-Applicant Paul Weigel, includes as attachments copies of the original manuscript submitted to the Journal of Biological Chemistry on July 23, 1999, the reviewer's comments, and the resubmitted manuscript as well as a

letter to the Editor establishing the changes made to the manuscript. It is obvious that the original manuscript demonstrates conception and constructive reduction to practice of the presently claimed invention, and that the minor revisions made to the manuscript were simply to further exemplify and clarify information originally submitted. In addition, the declaration further establishes conception and constructive reduction to practice of the presently claimed invention at least as early as April 26, 1999, as evidenced by a prior manuscript submitted to Biochemistry, which is also attached to the Declaration.

Therefore, Applicants respectfully submit that the 37 C.F.R. 1.131 declaration submitted herewith clearly demonstrates conception and constructive reduction to practice of the present invention prior to the publication date of the McCourt et al. reference. Therefore, Applicants respectfully submit that McCourt et al. is not a proper reference under 35 U.S.C. 102(a)/103(a).

Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. 102(a)/103(a) rejection of pending claims 24, 42 and 88 over McCourt et al.

Applicants' Response to the 35 U.S.C. 102(b)/103(a) Rejection of the Claims

In the Office Action, the Examiner maintained the rejection of Applicants' claims 24, 42 and 88 under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Yannariello-Brown et al.

(Glycobiology 7:15). Applicants respectfully traverse the rejection of pending claims 24, 42 and 88, as now amended, for the reasons stated herein below.

Claims 24, 42 and 88, as now amended, recite a purified mammalian HARE comprising a protein which is able to specifically bind at least one of HA, chondroitin and chondroitin sulfate or a purified composition comprising a functionally active HARE polypeptide, wherein the protein or functionally active HARE polypeptide is purified to a state capable of being sequenced and comprises a sequence having at least about 76% sequence identity to SEQ ID NO:2. The purified mammalian HARE protein may have a molecular mass in a range of from about 175 kDa to about 190 kDa.

Yannariello-Brown et al. describe the identification of a 175 kDa protein in rat liver endothelial cells (LEC) that binds HA. LEC membrane extracts were separated by nonreducing SDS-PAGE and ligand blotted with ^{125}I-HA to identify HA-binding proteins, and a polypeptide having an M_r value of ~175,000 was identified. The extracts were also subjected to gel filtration chromatography, and fractions containing HA-binding activity were pooled to enrich the 175 kDa protein having HA-binding activity. However, this pool contained a large number of proteins that were not clearly separable by denaturing SDS-PAGE (see Fig. 5B, S400 POOLS, lane 1). While the 175 kDa protein was "enriched" in this pool as compared with the LEC membrane extracts, the Yannariello-Brown et al. reference does not disclose, teach or suggest a protein "purified to a state capable of being sequenced", as recited in the claims of the subject

application.

Considering the number of proteins present in the SDS-PAGE gel of FIG. 5B of Yannariello-Brown et al., removal of a section of membrane that contains only the protein of interest would be virtually impossible. Indeed, the inventors attempted classical biochemical purification techniques, such as those described in the Yannariello-Brown et al. reference, in diligent attempts to purify the rat liver HA receptor for sequencing. As described in the 37 C.F.R. 1.132 declaration submitted by co-inventor Paul Weigel on February 13, 2003, such attempts were unsuccessful. This is due in part to the large number of receptor proteins that have similar molecular weights and electrophoretic properties. In fact, at one point the inventors believed that a high enough degree of purity had been obtained to send a protein sample for N-terminal amino acid sequence, but the sequence obtained was a match for the mannose receptor, which is a membrane protein having a similar size to that of the 175 kDa HARE (see Page 3, ¶2 of the Declaration).

In addition, the "enriched" proteins shown on the SDS-PAGE gel of FIG. 5B of Yannariello-Brown et al. do not meet the claim limitations of being "functionally active" or "able to specifically bind at least one of HA, chondroitin and chondroitin sulfate", as such proteins were subjected to denaturing conditions in the process of preparing and running the SDS-PAGE gel. Thus, the proteins illustrated in FIG. 5B of Yannariello-Brown et al. do not function as claimed in amended claims 24, 42 and 88 of the subject application.

Therefore, Applicants respectfully submit that claims 24, 42 and 88, as now amended, are neither anticipated by nor obvious over the Yannariello-Brown et al. reference. Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. 102(b)/103(a) rejection of pending claims 24, 42 and 88 over Yannariello-Brown et al.

In addition, Applicants respectfully submit that newly added claims 89-93, 94-98 and 99-103, which depend from claims 24, 42 and 88, respectively, are not anticipated by nor obvious over Yannariello-Brown et al. Applicants also respectfully submit that newly added claims 104-115, which recite a purified mammalian HARE protein wherein the protein is substantially free of other proteins, are also not anticipated by nor obvious over Yannariello-Brown et al., as Yannariello-Brown et al. only teach fractions containing multiple proteins, and do not teach, disclose or suggest a purified mammalian HARE protein substantially free of other proteins. Further, Applicants also respectfully submit that newly added claims 116-134, which recite a recombinant mammalian HARE protein, are also not anticipated by nor obvious over Yannariello-Brown et al., because Yannariello-Brown et al. do not teach, disclose or suggest recombinant proteins.

Summary of the Interview

An interview was held on October 8, 2003, between the Examiner and Applicants' representatives Douglas Sorocco, Kathryn Hester and Mike Smith.

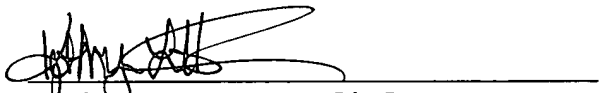
In the interview, claims 24, 42 and 88 and the Yannariello-Brown et al. and McCourt references were discussed. In the interview, (1) Applicants' representatives agreed to amend claims to recite measures of identity or other limits to overcome the 35 U.S.C. 112, ¶1 rejection; (2) Applicants intend to introduce biological deposit information; and (3) a new declaration would be submitted to overcome the McCourt reference. In discussing the Yannariello-Brown reference, the possibilities of product-by-process type claims or claim language such as "free from other rat proteins" was discussed, as well as trying to demonstrate that the protein of Yannariello-Brown was inactive.

CONCLUSION

This is meant to be a complete response to the Office Action mailed April 25, 2003 and a Summary of the Interview held on October 8, 2003. Applicant respectfully submits that each and every rejection of pending claims 24, 42 and 88, as now amended, has been overcome, and that such claims are now in a condition for allowance. Further, Applicant respectfully submits that newly added claims 89-134 are allowable over the art of record. Favorable action is respectfully requested.

Should the Examiner have any questions or comments concerning the before-mentioned amendments to the application or any other matter, Applicant's agent will welcome the opportunity to discuss same with the Examiner.

Respectfully submitted,



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